

PERSPECTIVES IN PHYSIOLOGY

Disinhibition and brain rhythms

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Rhythmic activity is one of the striking hallmarks of the central nervous system and was first detected when EEG techniques were pioneered over 60 years ago. Various behavioural states and several brain regions are associated with distinctive oscillatory patterns. For example, the θ rhythm, which is characterized by 5–10 Hz oscillations, has been observed in several regions of the limbic brain, including the septum where it is thought to be generated, and the hippocampus and entorhinal cortex (Bland, 1986). θ activity occurs in awake behaving rats when the animal explores a novel environment. Stimulation of hippocampal pathways at θ frequencies is particularly effective in inducing long-term potentiation suggesting that θ oscillations are important in memory mechanisms. However, despite years of study, the cellular and synaptic mechanisms underlying the generation of the widespread rhythmic synchronization characteristic of θ have proved elusive. An article by Tóth *et al.* (1997) in this issue of *The Journal of Physiology* provides an important insight into the synchronizing mechanism underlying θ . The results of Tóth *et al.* (1997) suggest that an interplay between the GABAergic interneurons of the septum and the hippocampus is critical in the generation of θ . GABAergic septal projections are shown to inhibit hippocampal interneurons and thereby disinhibit pyramidal neurones. Stimulation of the septal inputs at θ rates induced a θ -like oscillation of pyramidal cells and reproduced a key feature of θ : out of phase activity of pyramidal neurones and inhibitory interneurons.

The beauty of this work is manifold. First, a new slice preparation was developed that maintained septal–hippocampal connectivity. The authors used a series of freehand razor cuts so that the final slices cut on the vibratome contained axonal projections that curved in three-dimensional space. This may be a trivial problem to mathematicians but to neurobiologists this is a clever piece of work. Second, this work addresses a functional hypothesis first posed by one of the authors as a result of his anatomical observations years ago. In an elegant study in 1988, Freund & Antal described projections of the septum to hippocampal interneurons which were postulated to control inhibition in the hippocampus. The article in

this issue (Tóth *et al.* 1997) which Freund co-authored demonstrates that his original prediction was correct.

There are two key questions that have to be addressed in any study of the cellular and synaptic mechanisms of rhythm generation. The first is how is patterned activity generated and the second is how are these patterns synchronized among separated regions of the brain. The article by Tóth *et al.* (1997) illustrates a mechanism that could be important in the synchronization between two separate regions, the septum and the hippocampus. Their results provide an important contribution to our understanding of the synchronizing mechanisms underlying θ because they demonstrate that GABAergic projections from the septum directly inhibit hippocampal interneurons. However, there are also cholinergic projections from septal neurones that have to be considered in any complete model of θ generation. These cholinergic septal projections are known to increase the excitability of pyramidal neurones by modulating several ionic conductances. There are also other contributors to oscillatory activity in addition to rhythmic GABAergic disinhibition. The intrinsic oscillatory properties of the hippocampus and entorhinal cortex most probably act in concert with the septal GABAergic projections to generate rhythmic activity because both these structures can resonate at θ frequencies even when isolated from the septum. For example, synchronous 5–8 Hz oscillations with some similarities to θ are observed following muscarinic stimulation in isolated hippocampal slices with no septal connections (MacVicar & Tse, 1989). Also, pyramidal neurones in the entorhinal cortex

can oscillate at θ frequencies when depolarized by current injection because of intrinsically generated low threshold Na^+ currents. Finally, the source of the rhythmic activity in the septal GABAergic neurones has to be studied further although there is evidence that septal neurones have intrinsic oscillatory properties (Alonso *et al.* 1996).

θ therefore might result from distributed oscillators that have the intrinsic ability to oscillate but are entrained by septal GABAergic projections. This would be consistent with the observation that θ can be observed in septal-lesioned animals. The results in Tóth *et al.* (1997) provide the first physiological evidence that the septal GABAergic projections to hippocampal interneurons generate and synchronize θ oscillations in these widely separated regions through rhythmic disinhibition.

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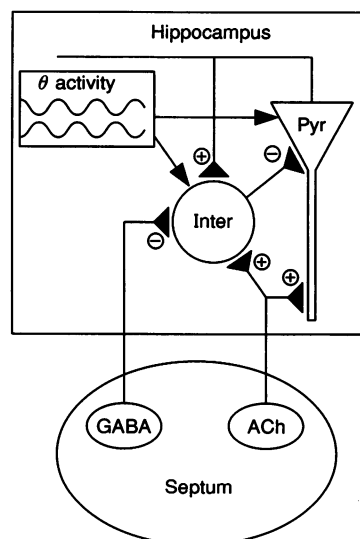


Figure 1. Septal connections disinhibit pyramidal neurones by directly inhibiting hippocampal interneurons

θ activity in the hippocampus is postulated in the article by Tóth *et al.* (1997) to be synchronized by the rhythmic disinhibition of pyramidal neurones (Pyr) by the septal GABAergic projections to hippocampal interneurons (Inter). This could explain the observed phase differences between depolarization and activity in pyramidal neurones and interneurons during θ . Septal cholinergic connections also serve to increase intrinsic neuronal excitability in the hippocampus.